Genetic Regulation of Behavioral and Physiological Sensitivity to Nicotine

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Numerous studies have demonstrated that the administration of an acute dose of nicotine results in alterations in a broad spectrum of behavioral and physiological measures. At least for some measures, both stimulant and depressant effects may be observed. This complexity has frustrated investigations that have been directed towards understanding the neurochemical measures that regulate nicotine response.

Our research group has chosen to use genetic strategies to attempt to broaden our understanding of those mechanisms that regulate the sensitivity of mice to nicotine. These strategies have involved an analysis of the relative sensitivities of a large number (19) of inbred mouse strains to nicotine. Most of our studies have assessed the effects elicited by injection with low doses of nicotine on rate of respiration, locomotor activities measured in either a Y-maze or an open-field arena, acoustic startle response, heart rate and body temperature. We have also studied nicotine-induced seizures. In all cases, differences among inbred mouse strains have been detected. However, a mouse strain that was sensitive to one effect of nicotine or measured by an ED_{50} value was not necessarily sensitive to all other nicotine effects. Correlational and principal component analyses indicate that a minimum of two major families of responses to nicotine exist. One factor loads heavily on nicotine effects on locomotor activities and body temperature and another factor loads heavily on seizures. Nicotine effects on the other measures seem to be regulated by both of the major factors. The numbers and affinities of L-[^{3}H]nicotine and α-[^{125}I] bungarotoxin were also measured in eight brain regions. Mouse strains differ in the number, but not the affinities, of both of these binding sites. The two binding sites segregated independently of one another suggesting separate genetic control. Correlation between sensitivities to nicotine and nicotinic receptor numbers were calculated and significant correlations (r = approximately 0.6) were found between nicotine effects on locomotor activities and body temperature and [^{3}H] nicotine binding on one hand and nicotine-induced seizures and α-[^{125}I]bungarotoxin binding on the other hand.

More recent studies have focused on corticosteroid regulation of sensitivity to nicotine and on nicotinic receptor binding. Only a few strains have been analyzed to date but the results available clearly demonstrate that inbred mouse strains differ in the effects of adrenalectomy and corticosterone on sensitivity to nicotine. Data currently on hand indicate that corticosterone inhibits binding to brain nicotinic receptors in several mouse strains. Whether this inhibition varies between mouse strains is currently under investigation.

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